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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,808	04/21/2006	Dearg Sutherland Brown	056291-5279	9921

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
WARD, PAUL V	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,808	BROWN ET AL.	
	Examiner	Art Unit	
	PAUL V. WARD	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/09 4/20/07 10/2/06 4/21 06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of re the Restriction/Election requirement in the reply filed on May 18, 2009 is acknowledged, and is found persuasive. Thus, the election requirement is withdrawn.

An action on the merits on claims 1-14 and 17-20 is contained herein.

Information Disclosure Statement

Receipt of the information disclosure statements filed April 20, 2007, October 2, 2006, April 21, 2006 and May 18, 2009 is acknowledged, and copies are enclosed herewith.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and those claims dependent thereon are rejected because the claims define variables (where applicable) as heteroaryl, heterocyclyl, heteroaryl-alkoxy, heteroaryloxy, heteroaryloxy, heterocyclyoxy, heterocyclylamino". The terms are indefinite since the specification does not define the ring size, heteroatom, number and nature of substituents, and the exact point of contact with the atom(s) for the substituents. Correction is required.

Claim 14 is indefinite for reciting "any functional group is optionally protected". It is not understood which functional group Applicant is intended? Is it the hydroxl group? Is it the ketone group? Is it the carboxyl group? Correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claims 17-19 are rejected because the specification, while being enabling for the treatment of certain diseases that are mediated by cytokines, does not provide enablement for all cytokine mediated diseases. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

1) Nature of the invention.

The nature of the invention in claims 17-19 is the treatment of all cytokine mediated diseases, for example inflammatory and allergic diseases, psoriasis and pulmonary diseases.

2) State of the prior art and the predictability or lack thereof in the art.

The art pertaining to the treatment of all cytokine mediated diseases remain highly unpredictable. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of cytokine-mediated diseases, whether the cytokine was promoted or inhibited would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the disease claimed as capable of treatment by the compound of claimed, and the inhibition of cytokine, one of skill in the art is unable to fully predict possible results from the administration of the compound claimed due to the unpredictability of the role of

cytokine, i.e., whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine what listed diseases would be benefited by the inhibition of cytokine and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of cytokine.

4) Amount of direction and guidance provided by the inventor.

The applicant has not demonstrated sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to the same in the prior art to provide a skilled artisan with sufficient guidance to practice the instant treatment of diseases listed as cytokine-mediated diseases. Further, the applicant discloses that an effective amount of the compound will be administered without providing any direction other than that the compounds of the invention have a high

therapeutic index and follows this with a definition readily found in a basic pharmacology textbook. It should be noted that the therapeutic index of a drug in humans is almost never known and is only determined through clinical experience. Additionally, the specification is silent and fails to provide guidance as to whether the diseases listed as cytokine-mediated diseases require the inhibition of cytokine or the promotion of cytokine for treatment, i.e., the specification fails to provide a correlation between the diseases listed and the inhibition of cytokine.

5) Existence of working examples.

There is not seen in the disclosure, sufficient evidence to support Applicant's claims of treating all cytokine mediated diseases. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to treating all cytokine mediated diseases. There are not sufficient working examples or data from references of the prior art to provide a nexus between those examples and a method of treating all cytokine mediated diseases with the claimed compound.

6) Breadth of claims.

The breath of the claims is that the compounds claimed can treat any cytokine-mediated disease, without regards as to the affect of cytokine on the stated diseases.

7) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, it can be safely concluded that the instant case fails to provide an enabling disclosure for treatment of all cytokine mediated diseases.

3. Claims 20 are directed to a method of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders. The terms are interpreted to include any and all forms of obesity, type II diabetes, reducing weight, metabolic syndrome and sexual disorders. In light of this, it can be asserted that in spite of the vast expenditure of human and capital resources in recent years, no one drug has been found which is effective in treating all types of obesity, type II diabetes, reducing weight, metabolic syndrome and sexual disorders. In re Hokum, 226 USPQ 353 (ComrPats 1985).

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue".

These factors include, but are not limited to:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is seen to encompass methods for treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders by administering to a patient in need of such treatment a therapeutically effective amount of the compound claim. Applicant failed to exactly define what types of obesity, type II diabetes, reducing weight, metabolic syndrome and sexual disorders are treated. Thus, the claims are extremely broad.

The nature of the invention

The nature of the invention is the treatment of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders through the use of the claimed compound and derivatives thereof. Currently, there are no known agents that treat these diseases all inclusively.

The level of predictability in the art

The treatment of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders is highly unpredictable. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Additionally, it is the state of the prior art that AIDS is the result of an infection with the human immunodeficiency virus (HIV). This virus attacks selected cells of the immune, nervous, and other systems and impairs their proper function. HIV infection may cause damage to the brain and complications vary widely from one patient to another. There is no cure for AIDS but recently developed treatments help to slow the progression of the disease. Some neurological symptoms and complications may improve with treatment. In the absence of a showing of correlation between all the disorders claimed, which includes AIDS related, one of skill in the art is unable to fully

predict possible results from the administration of a compound claimed due to the unpredictability of the role of the compound.

The amount of direction provided by the inventor.

The applicant has not demonstrated sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or reference to the same in the prior art to provide a skilled artisan with sufficient guidance to practice the instant treatment of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders claimed. Further, the applicant discloses that an effective amount of the compound will be administered without providing any direction other than that the compounds of the invention have a high therapeutic index and follows this with a definition readily found in a basic pharmacology textbook. It should be noted that the therapeutic index of a drug in humans is almost never known and is only determined through clinical experience.

The existence of working examples.

There is not seen in the disclosure, sufficient evidence to support Applicant's claims of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 27 USPQ2d 1510

(CAFC). The disclosure does not demonstrate sufficient evidence to support the applicant's claim to the treatment and methods in inhibition. There are not sufficient working examples or data from references of the prior art to provide a nexus between those examples and a method of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders with the claimed compound.

The level of one of ordinary skill.

The level of skill is that of one with a doctoral understanding of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders therapeutics. Applicant's data is not convincing as to make the production and use of pharmaceutical compositions comprising the recited compounds feasible without undue, un-predictable experimentation.

The quantity of experimentation.

A great deal of experimentation is required. In order for there to be a method of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders generally, as claimed by the applicant, it would be necessary to show that a vast range of different types of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders. Furthermore, direction, in the form of examples, must be shown to determine what an effective dose may be. The references submitted do not

demonstrate this. Therefore, one of ordinary skill in the art would require a significant amount of experimentation in order to determine the effective dosage to treat the multitudes of different types of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders with the claimed compound individually or in combination with other therapeutic agents.

Thus, it can be safely concluded that the instant case fails to provide an enabling disclosure for the treatment of treating rheumatoid arthritis, asthma, COPD, inflammatory bowel disease, MS, AIDS, septic shock, congestive heart failure, ischaemic heart disease and psoriasis disorders.

Allowable Subject Matter

Claims 1-14 will be allowed if amended to overcome the rejections under 35 USC 112, second paragraph. The compounds in Claims 1-13 and the process in claim 14 were not found to be obvious nor anticipated by the prior art of record. The closest prior art, WO 00/55153, contains heterocyclic substituents correlating to Applicants R^4 moiety, which differs from the R^4 cycloalkyl substitutents as instantly claimed. Thus, the prior art does not teach or suggest the presently claimed compounds. Therefore, these claims will be allowed if amended to overcome the rejections under 35 USC 112, second paragraph.

Conclusion

Claims 1-14 and 17-20 are pending. Claims 1-14 and 17-20 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL V WARD whose telephone number is 571-272-2909. The examiner can normally be reached on M-F 8 am to 4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/PAUL V WARD/
Examiner, Art Unit 1624